

STATE-OF-THE-ART PAPER

Therapy for ST-Segment Elevation Myocardial Infarction Patients Who Present Late or Are Ineligible for Reperfusion Therapy

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Despite the wide contemporary availability of pharmacological and mechanical means of reperfusion, a very significant proportion of ST-segment elevation myocardial infarction (STEMI) patients are still not offered any reperfusion therapy, and some of them are considered “ineligible for reperfusion.” Spontaneous reperfusion and contraindications to the use of fibrinolytics and/or mechanical reperfusion methods account only for a small part of these clinical situations. The boundary between “timely” and “late” presentation in STEMI, the appropriateness of percutaneous intervention in patients presenting late after onset of symptoms, and the impact of sex and age on the eligibility and/or choice of reperfusion therapy continue to be challenged by the most recent published data. In the current invasive-driven reperfusion era, if scientific evidence and clinical guidelines are applied diligently, the vast majority of eligible STEMI patients should receive reperfusion therapy. Pharmacological nonlytic therapy of patients with STEMI, regardless of the choice of reperfusion strategy or the absence of it, is clearly defined by the current practice guidelines. Available data suggest that for patients who do not receive any form of reperfusion, anticoagulation therapy with low molecular weight heparin provides a clear additional mortality benefit versus placebo. Fondaparinux as compared with usual care (unfractionated heparin infusion or placebo) significantly reduces the composite of death or myocardial reinfarction without increasing severe bleeding or number of strokes. In the treatment of late-presenting patients with STEMI (beyond the first 12 h after onset of symptoms), clinical evaluation and risk stratification represent the crucial elements helping in decision making between therapeutic interventions. (J Am Coll Cardiol 2010; 55:1895–906) © 2010 by the American College of Cardiology Foundation

The most severe form of acute coronary syndrome (ACS) after sudden cardiac death is ST-segment elevation myocardial infarction (STEMI). According to the NRMI-4 (Fourth National Registry of Myocardial Infarction), 29% of infarction patients experience a STEMI (1), whereas a European survey, the EHS-ACS-II (Second Euro Heart Survey on Acute Coronary Syndromes), reported that 47% of ACS patients present with STEMI (2).

Prompt and complete coronary reperfusion using fibrinolysis or primary percutaneous coronary intervention (PCI) is the goal in STEMI, to reduce infarct size, adverse outcomes, and mortality. Current guidelines advocate attempting reperfusion therapy for all STEMI patients presenting within 12 h of symptom onset (3–5), and a recent analysis from the GRACE (Global Registry of Acute Coronary Events) shows that primary PCI is

rapidly becoming the preferred approach (6). However, a significant proportion of STEMI patients are not offered any reperfusion therapy, and a small fraction of STEMI patients are considered “ineligible for reperfusion.” In this review, we will describe the burden of “STEMI with no reperfusion therapy” and its causes, and review the data on antithrombotic and nonantithrombotic therapies (work-reducing and others) used in “no-reperfusion therapy” patients.

STEMI With No-Reperfusion Therapy

Magnitude of the Problem

Undertreatment. In the era preceding the widespread use of primary PCI, the German MITRA (Maximal Individual Therapy in Acute Myocardial Infarction) registry reported that no-reperfusion therapy was offered to 42.2% of patients with STEMI presenting within 48 h from symptom onset (7), whereas the French ACS registry from year 2000 reported that only 53% of STEMI patients presenting within 5 h of symptoms received reperfusion (8). In the EHS study, only 56% of STEMI patients received reperfusion therapy (35% with fibrinolytic agents, 21% with primary PCI) (9). Among 8,305 patients with STEMI in the ACOS (Acute Coronary

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Manuscript received September 14, 2009; revised manuscript received November 18, 2009, accepted November 19, 2009.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor

ACS = acute coronary syndrome

ASA = acetylsalicylic acid

CI = confidence interval

LMWH = low molecular weight heparin

MI = myocardial infarction

OR = odds ratio

PCI = percutaneous coronary intervention

RRR = relative risk reduction

SR = spontaneous reperfusion

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

UFH = unfractionated heparin

Syndrome) registry, 28.3% did not receive any form of reperfusion (10). Between 2001 and 2002, in the TETAMI (Treatment With Enoxapam and Tirofiban in Acute Myocardial Infarction) randomized trial and registry, 28% of patients presenting within 12 h from onset of symptoms did not receive reperfusion therapy (11). Unfortunately, in the largest study to date of patients with STEMI (12), only half of the patients presenting within 24 h and not treated with mechanical reperfusion received fibrinolytic drugs. More recently, some progress has been made. In 2006, 33% of the GRACE patients presenting within 12 h of STEMI received no reperfusion (Fig. 1) (6). In the NRM1 registry, the proportion of patients with STEMI eligible for but not receiving any form of reperfusion therapy slowly decreased from 1992, but remained as high as 28.1% in 2006 (Fig. 2) (13). A similar pattern was also seen in the more recent OASIS-6 (Sixth Organization to Assess Strategies in Acute Ischemic Syndromes) trial (23.7% of patients not receiving reperfusion) (14).

What are the clinical outcomes of patients encountering “missed opportunities” for reperfusion? Most clinical trials exclude these patients from their analyses. The few studies focusing on this topic demonstrate that the lack of reperfusion therapy translates into worse outcomes. In the TETAMI registry, 30-day mortality was only 4.4% in patients who received reperfusion therapy, but 12% in patients who did not receive it. Similarly, the triple end point of death, myocardial reinfarction, or recurrent angina occurred in only 11% of patients receiving reperfusion compared with 19.1% of patients who did not (Fig. 3). In the ACOS registry, in-hospital mortality was 14% among patients not receiving reperfusion and only 6.3% among patients receiving reperfusion (10).

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Variables Associated With No-Reperfusion Therapy

Why do so many patients presenting with STEMI within 12 h from onset of symptoms not receive any reperfusion therapy? Spontaneous reperfusion and contraindications to the use of fibrinolytics and/or mechanical reperfusion account for a part of these clinical situations. In reality, these entities represent only a small fraction of the untreated patients. Another important association with no-reperfusion therapy is represented by patients who present between 12 and 24 h or later after the debut of symptoms. By the time many of these patients present to the hospital, their symptoms

have diminished, and many are hemodynamically and electrically stable. The current STEMI guidelines do not recommend attempting mechanical or pharmacological reperfusion in such “late” and stable patients. Figure 4 summarizes the various clinical scenarios that can occur in the setting of STEMI and the available therapeutic options.

Patients presenting <12 h from onset of symptoms.
SPONTANEOUS REPERFUSION. Spontaneous reperfusion (SR) is a well-recognized scenario in STEMI, but its incidence varies widely (4% to 57%) in different reports (15–17). In a study of 710 STEMI patients eligible for reperfusion (15), SR (defined as $\geq 70\%$ resolution of the cumulative ST-segment elevation compared with the initial electrocardiogram, and $>70\%$ reduction in pain) was observed in 155 (22%). The outcomes of patients with SR were better than those of patients without SR. On multivariate analysis, SR was significantly associated with a lower incidence of the composite of 30-day mortality, congestive heart failure, and recurrent ACS. In a pre-specified subgroup analysis of the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial (16), SR defined as angiographic TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 in the culprit vessel before PCI (first contrast injection), occurred in 11.5% of patients, and more commonly in nondiabetic patients. Nondiabetic patients with SR showed significant improvement in 90-day composite outcome of death, shock, or congestive heart failure versus without SR (4.0% vs. 8.9%, $p = 0.001$). A systematic analysis of the occurrence and prognostic implications of SR using electrocardiographic and angiographic assessments was done in a substudy of the ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction-4) PCI trial in 585 patients with STEMI randomized into the primary PCI arm (17). The SR assessed by $\geq 70\%$ cumulative ST-segment elevation resolution or by TIMI flow grade 3 in the infarct-related artery before PCI as comparable (14.9% vs. 14.7%). However, only electrocardiographic SR was associated with a lower mortality, whereas no such differences were evident in patients with angiographic SR versus no SR. This finding supports the concept that resolution of ST-segment elevation reflects both the recanalization of the culprit epicardial vessel and a better microvascular flow at the cellular level (18).

CONTRAINDICATIONS. Absolute and relative contraindications for fibrinolysis are clearly defined in the current STEMI clinical guidelines and are mostly related to the risk of intracerebral bleeding (3–5). The true incidence of these contraindications is rarely reported in clinical studies, but it is probably very low. In the TETAMI randomized trial, only 1.4% of eligible patients did not receive fibrinolytic therapy because of absolute contraindications, and 2.6% because of relative contraindications (19). Primary PCI rarely has contraindications, except for the fear of bleeding from the adjunctive antithrombotic therapy (20).

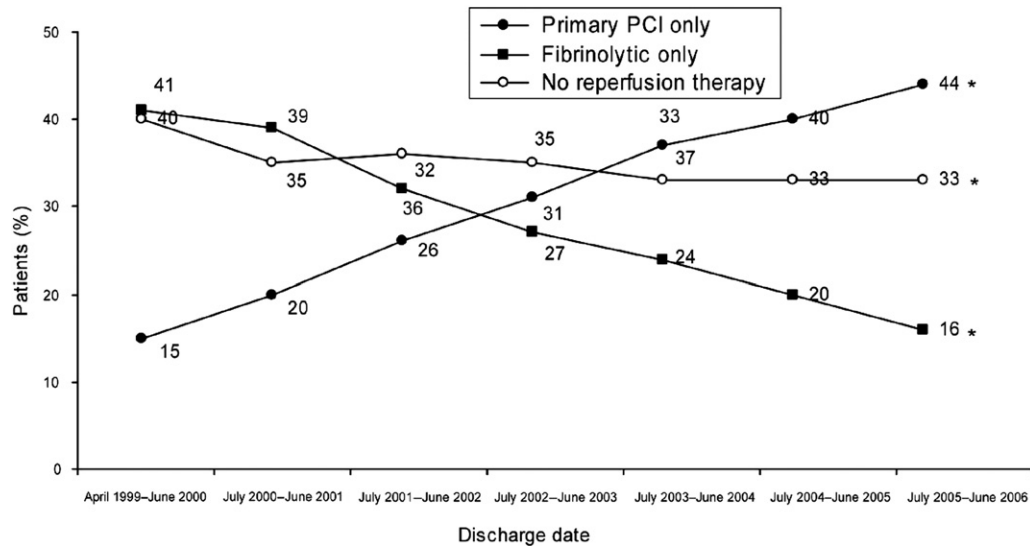


Figure 1 Use of Reperfusion Therapy From 1999 to 2006

The percentage of patients who received no reperfusion (open circles) decreased only from 40% in 1999 to 33% in 2006. During this interval, a continuous increase in the use of primary percutaneous coronary intervention (PCI) (solid circles), from 15% to 44%, was accompanied by a steady decline in the use of fibrinolysis (squares), from 41% to 16% (Cochran-Armitage test for linear trend, * $p < 0.0001$). Reproduced with permission from Eagle et al. (6).

Factors related to no-reperfusion therapy. An overwhelming majority of “eligible, but not receiving reperfusion therapy” patients do not have SR or contraindications. In a 2002 GRACE analysis (21), 4 factors were found to be strongly related (odds ratio [OR]: >2.0) to failure to provide or receive reperfusion therapy in STEMI: age >75 years, prior congestive heart failure, prior myocardial infarction (MI), or prior coronary artery bypass surgery. Other variables associated with not offering reperfusion were female sex, diabetes, and delayed

presentation (6,21). Multivariate analysis of the combined TETAMI randomized trial and registry patients, revealed that delayed presentation (>12 h), age >75 years, systolic pressure <100 mm Hg, and geographic region were significant independent predictors of not receiving reperfusion therapy (22).

AGE. Elderly patients (>65 years of age) constitute one-half of the hospital admissions for STEMI and account for as many as 80% of STEMI deaths (23). Only 9% have absolute

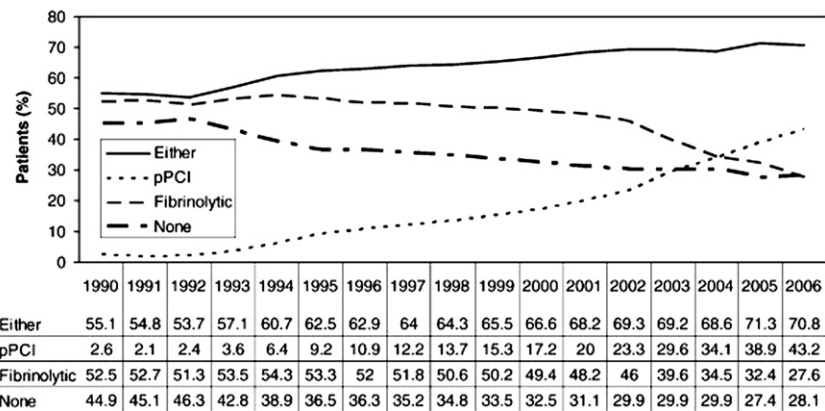


Figure 2 Trends in Type of Reperfusion Therapy Among Patients Eligible for Reperfusion From 1990 to 2006

The National Registry of Myocardial Infarction registry data demonstrate that the increased use of primary percutaneous coronary intervention (pPCI) (dotted line) parallels a steady increase in the percentage of patients who are offered reperfusion therapy; but even in 2006, approximately 30% of the patients with ST-segment elevation myocardial infarction did not receive any reperfusion intervention (dash-dot line). Since 2004, pPCI is the most prevalent method of reperfusion in these patients. Dashed line = fibrinolytic therapy; solid line = either. Reproduced with permission from Gibson et al. (13).

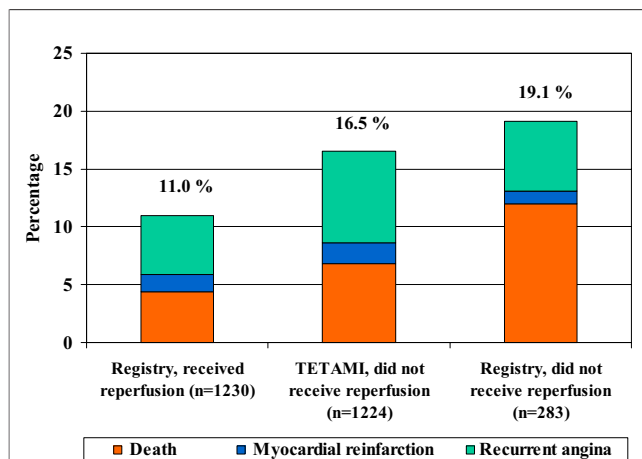


Figure 3 Clinical Event Rates at 30 Days, by Reperfusion Status in the TETAMI Registry and Trial

The absence of reperfusion therapy translates into significantly worse clinical outcomes, as illustrated by the triple end point of death (orange areas), myocardial reinfarction (blue areas), and recurrent angina (green areas). Mortality almost triples among the TETAMI (Treatment With Enoxaparin and Tirofiban in Acute Myocardial Infarction) registry patients who did not receive reperfusion. Reproduced with permission from Cohen et al. (11).

contraindications to fibrinolytic therapy (24). Nevertheless, the MITRA registry identified advanced age at presentation (>70 years) as 1 of the determinants of no-reperfusion therapy in STEMI (7). As mentioned in the preceding text,

the GRACE revealed that patients ≥ 75 years of age were less likely to receive reperfusion therapy (OR: 2.63, $p < 0.0001$, for younger vs. older than 75 years of age receiving reperfusion). Similarly, the TETAMI trial and registry found an OR of 0.425 for receiving reperfusion in STEMI patients >75 years of age (11).

In many STEMI trials, patients >75 years of age are outrightly excluded from enrollment. Even in trials without age restriction, there are fewer elderly patients compared to real-life age distribution of STEMI. A recent scientific statement on this topic reveals that in the VIGOUR (Virtual Coordinating Center for Global Collaborative Cardiovascular Research) pool of trials (comprising >100,000 patients with STEMI), only 14% were elderly, compared with the 25% to 30% in the NRMI and GRACE registries. Elderly patients present more often atypically, after longer delays, and with multiple comorbidities. Hence, they are often not considered for enrollment in clinical trials (25). To their credit, the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) investigators (26) enrolled 20,506 patients in the largest study to date of fibrinolysis in STEMI, and 2,532 (12.4%) were ≥ 75 years old. The patients received either streptokinase or a fibrin-specific lytic, and were randomly assigned to enoxaparin versus UFH. The trial demonstrated that, by adjusting the dose of anticoagulation therapy, the incidence of

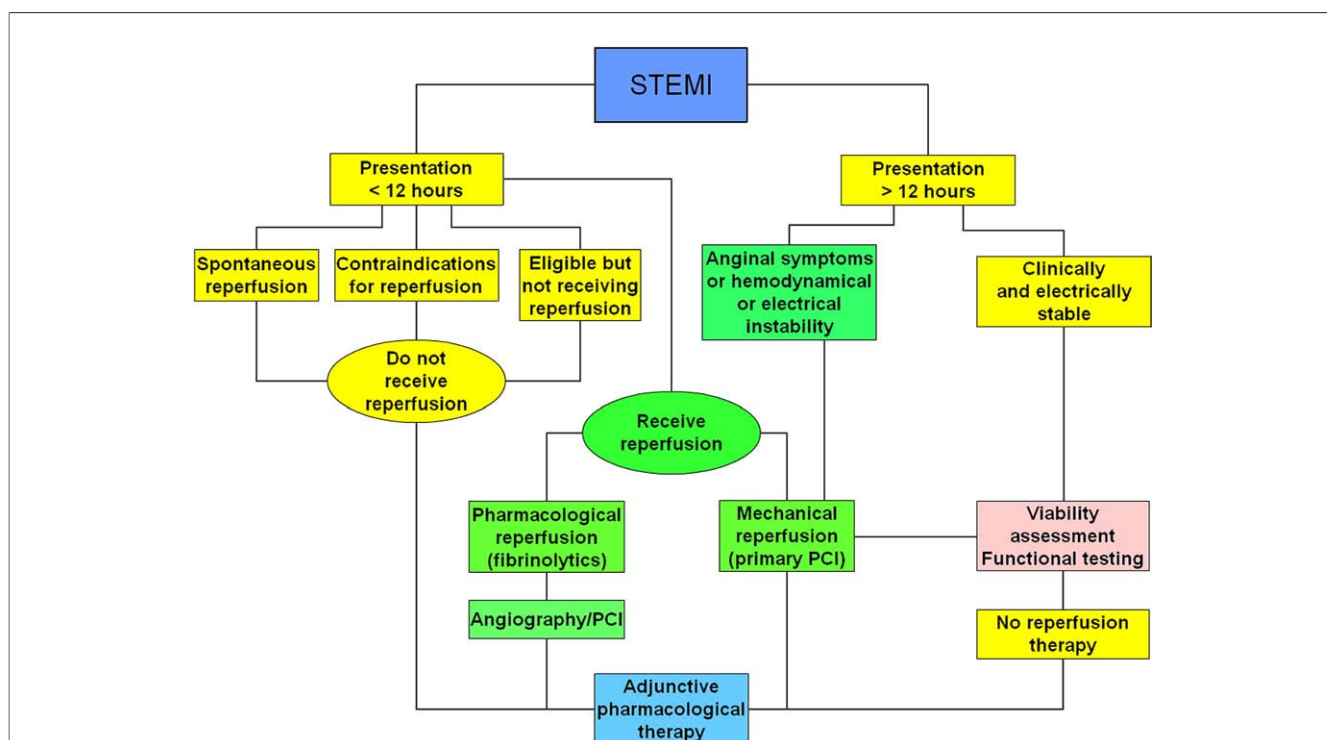


Figure 4 Spectrum of Clinical Scenarios and Therapeutic Options in STEMI

PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

major bleeding (2.9% with UFH and 3.3% with enoxaparin) and specifically intracranial hemorrhage (1.7% with UFH and 1.6% with enoxaparin) could be significantly minimized in elderly STEMI patients (26). That represents a significant advance when compared with previous lytic studies: in the ASSENT-3 and ASSENT-3 PLUS trials (analysis of combined data), the use of enoxaparin was associated with a rate of major bleeding of 5.2%, and of intracranial bleed of 6.7% among the patients 76 to 85 years old (27). The ExTRACT-TIMI 25 study demonstrated that fibrinolytic drugs can be safely used in the elderly provided that the adjunctive anticoagulant therapy is adjusted. In a study conducted with 483 patients with STEMI ages 75 to 85 years in Japan, 55% were treated with fibrinolytic agents (with a 92% rate of success) and 45% were offered “conservative therapy.” The pharmacological reperfusion strategy did not provide any clinical benefit in this trial, and the rate of cerebral hemorrhage was similar (28).

In the Senior PAMI (Primary Angioplasty and Thrombolytic Therapy in Elderly Patients With Acute Myocardial Infarction) trial (29), 481 patients >70 years of age presenting with STEMI within 12 h of symptoms were randomly assigned to PCI versus fibrinolytic therapy. There was a nonsignificant 36% reduction in death or nonfatal stroke (11.3% PCI vs. 13% thrombolytic therapy, $p = 0.57$), but a significant 55% reduction in death, stroke, or reinfarction favoring PCI (11.6% PCI vs. 18% thrombolytic therapy, $p < 0.05$). No difference between reperfusion strategies was seen in the subgroup of patients >80 years of age ($n = 131$). Similarly, the recent TRIANA (Tratamiento del Infarto Agudo de Miocardio en Ancianos) trial treated patients >75 years of age presenting with STEMI within 6 h with fibrinolytic therapy or primary PCI. The TRIANA study showed a significant advantage of primary PCI with regard to the secondary end point of recurrent ischemia (0.8% vs. 9.7%, $p < 0.001$ when compared with fibrinolysis) (30). There was a favorable trend toward reduction of the composite primary end point of death, reinfarction, or disabling stroke at 30 days with primary PCI, 18.9% versus 25.4% with fibrinolysis ($p = 0.21$). In a pooled analysis of 22 randomized trials of PCI versus fibrinolytic therapy, the PCAT-2 (Primary Coronary Angioplasty vs. Thrombolysis) investigators found that the absolute mortality advantage of PCI over fibrinolysis increased with age from 1% at 65 years to 6.9% at >85 years (31). The small number ($n = 56$) of patients >75 years of age with cardiogenic shock enrolled in the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial did not benefit from revascularization, prompting the guidelines’ recommendation for early revascularization only for patients <75 years of age. However, in the associated SHOCK registry, among patients >75 years of age, those who underwent early revascularization ($n = 44$) had a >50% lower mortality rate than those who did not ($n = 233$ [relative risk: 0.46, 95% confidence interval [CI]: 0.28 to

0.75, $p = 0.002$]) (32). Similarly, a trial of 88 very old patients (>85 years) with STEMI treated with primary PCI described good short- and long-term outcomes and identified age >90 years, late presentation, failed PCI (8% of patients), and Killip class III or IV (17%) as predictors of mortality at long-term follow-up (33). All these findings suggest that in the absence of life-threatening comorbidities, advanced age alone should not limit the use of reperfusion therapy for eligible elderly patients with STEMI.

SEX. Several studies suggest that female sex is associated with underutilization of reperfusion therapy. The MITRA registry showed that only 48.6% of women presenting with STEMI received any form of reperfusion (primarily thrombolysis) compared with 62.5% of men (OR: 0.83, $p < 0.002$), even among eligible patients. Women, on average, were 9 years older than men, had longer pre-hospital delays, and more comorbidities, which might have contributed to lower utilization of reperfusion. The multivariate, age-adjusted analysis of the MITRA registry demonstrated no difference in the long-term mortality between sexes (7). In the TETAMI randomized trial and registry, there was also a trend toward more men than women receiving reperfusion therapy (47.3% vs. 38.2%) (11). However, female sex was not retained as a predictor for not receiving reperfusion therapy after multivariate analysis (22). Similar to the MITRA registry, women in the TETAMI study were older, had higher Killip class at presentation, and presented later after symptom onset. More recently, the CRACE (Chinese Registry of Acute Coronary Events) showed that fewer females received reperfusion therapy compared with males (26.8% vs. 37.1%, $p = 0.013$) (34). The percentage of women ≥ 75 years of age (19.4%) was significantly higher than for men (12.1%, $p < 0.0001$); hence, an age-related bias may account for the underutilization of reperfusion strategies.

These findings suggest that female sex by itself is probably not directly associated with underutilization of reperfusion therapy, but rather the increased likelihood of women, as opposed to men, to present later after onset of symptoms, have more atypical symptoms, more advanced age, and more comorbidities accounts for their being less likely to receive reperfusion therapy.

NUMBER OF COMORBIDITIES. Identification of cardiac or noncardiac comorbidities in STEMI patients poses additional challenges to the physician considering reperfusion therapy. In a Canadian study, 73.5% of patients diagnosed with STEMI and eligible for reperfusion therapy received it (70.8% fibrinolysis and 2.6% primary PCI) (35). The adjusted probability of receiving any reperfusion therapy fell by 18% with each additional pre-existing condition (Fig. 5).

The AMI-Florence registry enrolled 740 patients presenting with STEMI within 12 h from the onset of symptoms. Only 63.5% of patients received reperfusion therapy (91.5% primary PCI) (36). Similar to the Canadian

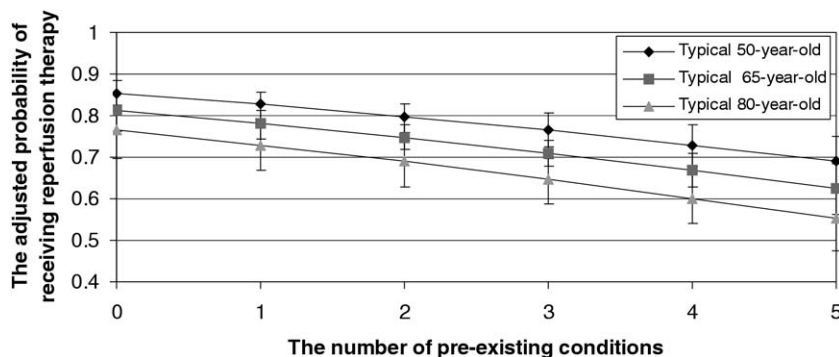


Figure 5 Adjusted Probability of Reperfusion Therapy According to Age and Number of Pre-Existing Conditions

The number of pre-existing conditions represents the cumulative sum of all cardiac and noncardiac comorbid conditions and is stratified according to the typical 50-year-old patient (diamonds), 65-year-old patient (squares), and 80-year-old patient (triangles). The probability of reperfusion therapy ($\pm 95\%$ confidence interval) is adjusted for age, sex, socioeconomic status, ethnicity, hospital type, rural-urban status, and hospital arrival times. $p = 0.001$ for the effects of age; $p < 0.001$ for the effect of the number of pre-existing conditions. Reproduced with permission from Parker et al. (35).

study, the proportion of patients receiving reperfusion progressively decreased with increasing chronic comorbidity, from 78.8% in the lowest tertile to 41.9% in the highest. At the same time, 1-year mortality was significantly reduced by the use of reperfusion in the highest tertile of chronic comorbidities (approximately 53% reduction) (Fig. 6). These examples illustrate the treatment-risk paradox applied to eligible STEMI patients: systematic underutilization of reperfusion therapy in sicker patients limits the opportunity of delivering the best treatment to the patients who will most benefit from it.

LATE PRESENTATION, >12 H FROM ONSET OF SYMPTOMS. The impact of the duration of symptoms on the decision to use a reperfusion-based strategy in STEMI has undergone extensive research. The most important element influencing outcomes in patients with STEMI is the time from symptom onset to reperfusion. The current guidelines strongly recommend reperfusion therapy for patients presenting within 12 h of symptoms. This time limit derives primarily from the early reperfusion trials using fibrinolytics, where the efficacy of thrombolytic therapy (the mortality benefit), demonstrated an important time-dependency. The GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico) trial demonstrated that the reduction in mortality with streptokinase decreased dramatically from 51% in patients treated within 1 h of symptoms onset, to only 20% if thrombolysis was performed between 3 and 6 h from the onset of symptoms (37); and the LATE (Late Assessment of Thrombolytic Efficacy) study (38) showed no benefit for thrombolytic therapy in STEMI if administered 12 to 24 h after the symptoms.

The impact of “later” arrival to hospital, even within 12 h, was described by an NRMI analysis: 77% of patients arriving within 1 h received some form of reperfusion therapy, versus only 46% for patients presenting 11 to 12 h from onset of

symptoms. Patients with longer delays between symptom onset and presentation also had longer door-to-balloon time (99 vs. 123 min) and door-to-needle time (33 vs. 47 min) (39). Incremental delays to mechanical reperfusion within the initial 12 h from the onset of symptoms also adversely impacts survival and myocardial recovery after primary PCI (Fig. 7) (40).

A few studies prospectively investigated the benefit of mechanical reperfusion beyond 12 h. The “open artery hypothesis” postulates that late mechanical recanalization after STEMI may prevent infarct expansion, electrical instability, and enhance collateral blood supply to other territories. In the OAT (Occluded Artery Trial), 2,166 stable patients with an occluded infarct-related artery identified 3 to 28 days after STEMI were randomly assigned to PCI or conservative therapy (41). At the 4-year follow-up, there were no differences between the groups in either the rate of the primary composite end point of death, reinfarction, or New York Heart Association functional class IV heart failure (17.2% vs. 15.6%, $p = 0.18$) or mortality (9.1% vs. 9.4%). Of note, 90% of the patients in the OAT who had a stress test before randomization had absent or only mild ischemia. Thus, the lack of benefit observed in utilizing PCI beyond 72 h from the index event in STEMI may be confined to patients without significant residual ischemia.

In contrast, the SWISSI-II (Swiss Interventional Study on Silent Ischemia Type II) study (42), performed in the pre-stenting era, supports the idea that for patients with recent STEMI in whom exercise stress imaging revealed silent ischemia, balloon angioplasty reduces the long-term rates of cardiac death, nonfatal MI, or symptom-driven revascularization, and improves functional capacity and left ventricular ejection fraction at 4 and 10 years. Thus, significant residual ischemia might still be present even in the absence of chest pain, frequently interpreted as a reflection of no active ischemia.

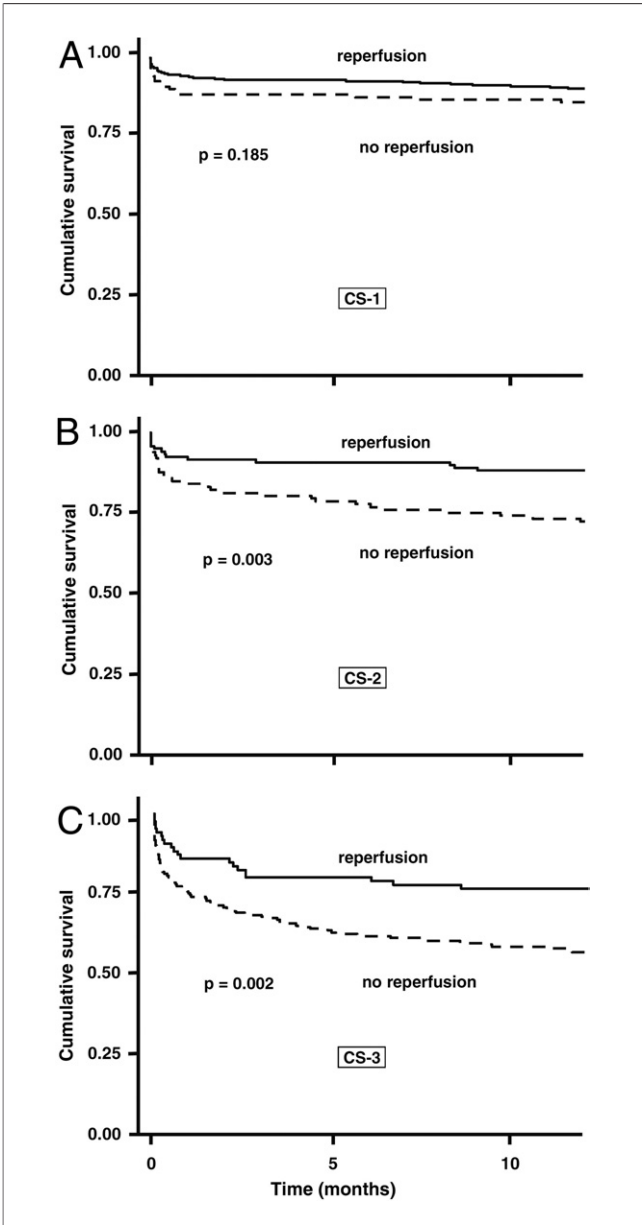


Figure 6

12-Month Cumulative Kaplan-Meier Survival Curves by Coronary Reperfusion Therapy Status and Chronic CS Category

Compared to a conservative approach, reperfusion therapy was not associated with a significant reduction in 12-month mortality in the group of patients with the least comorbidities (comorbidity score [CS]-1 [A], receiving reperfusion in 71.2% of cases). Even though used in a significantly lower percentage of patients in the groups with more comorbidities (CS-2 [B] 51.1%, and CS-3 [C] 32.1%), reperfusion therapy was associated with a progressively larger and significant reduction in 12-month mortality in these groups. Reproduced with permission from Balzi et al. (36).

STEMI With Nonreperfusion Therapy

Nonreperfusion therapeutic options for patients presenting late or considered ineligible for reperfusion therapy. While the current American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines for the management of all patients

with STEMI (3–5) recommend treatment with aspirin, thienopyridines, UFH or low molecular weight heparin (LMWH), beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and statins, unless otherwise contraindicated, there are currently limited published data specifically addressing the efficacy of these interventions in patients with STEMI who present late or are ineligible for reperfusion.

Antithrombotic therapy with platelet inhibitors. **ORAL AGENTS, ACETYLSALICYLIC ACID.** Platelet inhibition is the cornerstone of antithrombotic treatment in STEMI and has been shown to reduce mortality, with or without concomitant reperfusion therapy. The ISIS-2 (Second International Study of Infarct Survival) showed that aspirin alone in patients with acute MI conferred an absolute risk benefit in 35-day mortality of 2.4% (relative risk reduction [RRR] 23%) compared with no antithrombotic therapy (43). This was comparable to the benefit seen with streptokinase (Fig. 8). The current guidelines for the treatment of STEMI in patients with normal platelet counts suggest that acetylsalicylic acid (ASA) therapy is associated with an RRR in mortality rate of 20% to 25% regardless of whether patients

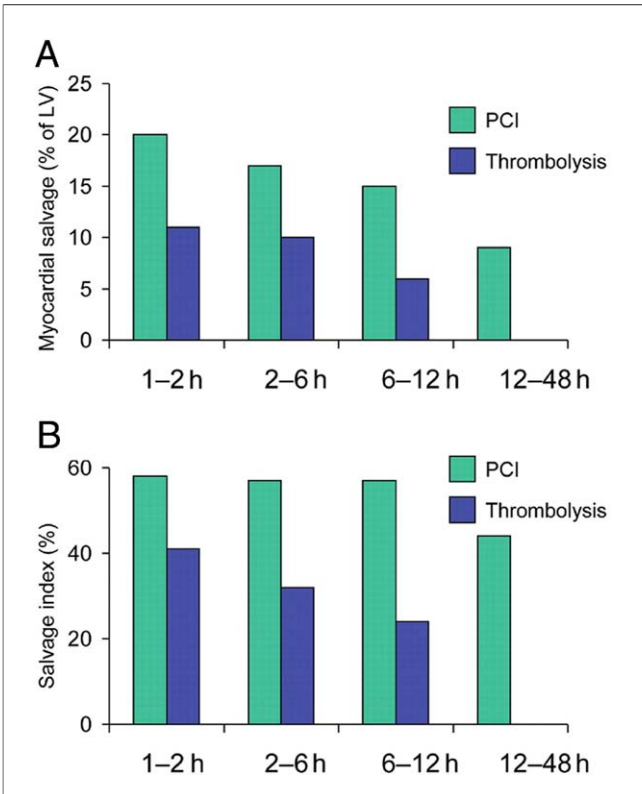


Figure 7

Time Dependence of Myocardial Salvage

Time dependence of myocardial salvage according to time-to-treatment interval in patients with ST-segment elevation myocardial infarction (STEMI) treated by percutaneous coronary intervention (PCI [green bars]) or thrombolysis (blue bars). (A) Myocardial salvage expressed as percentage of the left ventricle (LV). (B) Myocardial salvage expressed as proportion of the initial area at risk salvaged by reperfusion therapy. Reproduced with permission from Schomig et al. (40).

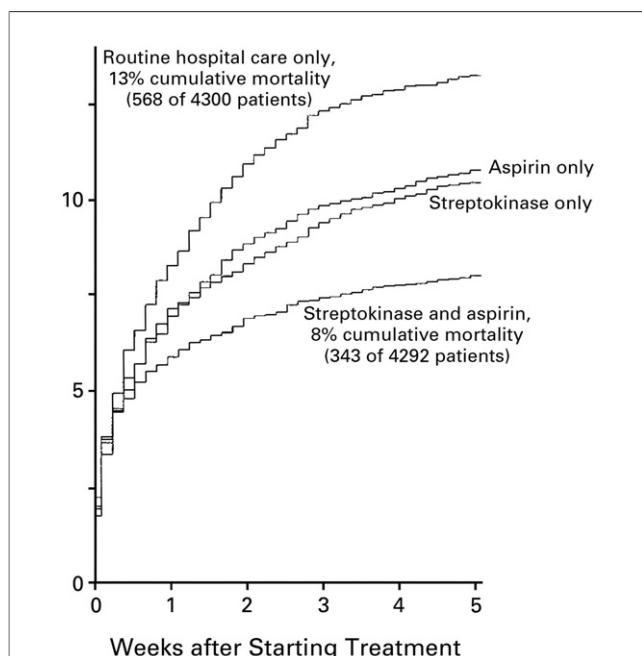


Figure 8 Mortality From Vascular Causes to 35 days in ISIS-2 Trial

Assignment to 1 month of treatment with aspirin produced a significant reduction of about one-fifth in mortality ($p < 0.001$), comparable to the use of streptokinase alone in this study. The effects of aspirin on overall mortality are similar whether or not patients receive fibrinolytic therapy or heparin. Reproduced with permission from the ISIS-2 (Second International Study of Infarct Survival) Collaborative Group (43).

are receiving reperfusion therapies (3–5). True aspirin hypersensitivity is the only exception. A dramatic insight into the role of ASA therapy is provided by cancer patients who present with ACS and thrombocytopenia, for whom ASA is often withheld because of fear of bleeding. In an observational study (44), the cancer patients diagnosed with ACS and having thrombocytopenia who did not receive ASA had a 7-day survival rate of only 6% compared with 90% for patients who received ASA ($p < 0.0001$). Patients with a platelet count $>100\,000$ cells/ μl who did not receive ASA had a 7-day survival rate of 45%, compared with 88% in patients who received ASA ($p = 0.01$). Use of ASA was not associated with more severe bleeding.

THIENOPYRIDINES. Clopidogrel is useful as a substitute for aspirin for patients with aspirin hypersensitivity (3–5), and is recommended for patients with STEMI undergoing reperfusion with either primary angioplasty or fibrinolysis.

What about the STEMI patients not receiving reperfusion therapies? The ACOS registry (45) studied the impact of clopidogrel in addition to aspirin on 1-year clinical outcomes of survivors of STEMI treated with or without reperfusion, and showed a reduction in major adverse cardiac and cerebrovascular events (death, nonfatal reinfarction, and nonfatal stroke) with added clopidogrel in all subgroups of patients (Fig. 9). The absolute

mortality benefit was greatest (8%) for the group of patients without early reperfusion therapy, who had the highest 1-year mortality (18%), but after multivariate analysis remained significant only in patients receiving reperfusion.

The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) evaluated aspirin plus clopidogrel for 4 weeks versus aspirin alone in 45,852 STEMI patients presenting within 24 h of STEMI (mean 10 h, 34% <6 h) (12); 43% of patients received no-reperfusion therapy. Compared with aspirin alone, dual-therapy recipients had significantly lower 30-day incidence of the composite end point of death, reinfarction, or stroke (9.2% vs. 10.1%, $p = 0.002$), and of death (7.5% vs. 8.1%, $p = 0.03$). Subgroup analysis showed similar reductions of the primary end point with clopidogrel irrespective of the use of fibrinolytic therapy (11% reduction with fibrinolytic therapy vs. 7% without).

Parenteral platelet inhibitors. GLYCOPROTEIN IIb/IIIa RECEPTOR BLOCKERS. The role of glycoprotein IIb/IIIa inhibitors in restoring perfusion was investigated either in combination with thrombolytics or as an adjunct to primary angioplasty. There are no data to support the use of intravenous glycoprotein IIb/IIIa inhibitors alone as an antiplatelet agent in the absence of reperfusion in STEMI. The TETAMI randomized trial (19) demonstrated that addition of tirofiban to either UFH or LMWH did not provide additional benefit regardless of the use of reperfusion.

Antithrombotic therapy with parenteral anticoagulants. UFH. Randomized data supporting the use of UFH in patients with acute MI, including STEMI, come from an earlier era in which patients were not routinely treated with

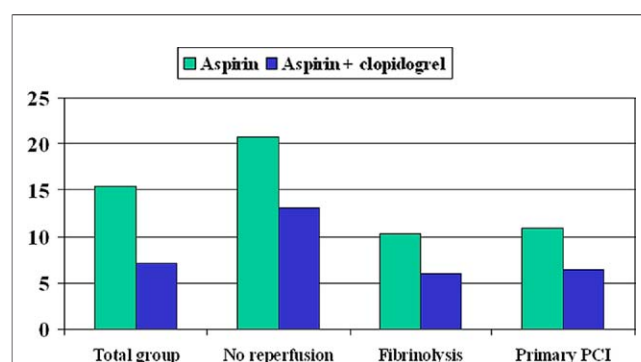


Figure 9 Incidence of MACCE After 1 Year Among Survivors of STEMI

Incidence of major adverse cardiac and cerebrovascular events (MACCE [death, nonfatal reinfarction, nonfatal stroke]) after 1 year in survivors of ST-segment elevation myocardial infarction (STEMI) treated with aspirin (green bars) or aspirin and clopidogrel (blue bars) at discharge. The reduction in mortality with clopidogrel was approximately 5% in both patients with fibrinolysis and primary percutaneous coronary intervention (PCI) and approximately 8% in patients without early reperfusion therapy. After multivariate analysis, the reduction of mortality remained significant only for patients receiving reperfusion. Acute Coronary Syndromes registry; reproduced with permission from Zeymer et al. (45).

aspirin and/or fibrinolytic therapy. The systematic overviews by Collins et al. (46,47) from all randomized trials (almost 73,000 patients in 26 trials) of early anticoagulation therapy for patients with suspected acute MI assessed the effects of adding UFH to aspirin or the effect of UFH alone on death and other major clinical events. In the trials with no concomitant aspirin, roughly 14% were given fibrinolytic therapy, whereas in trials with concomitant aspirin (almost 68,000 patients in 6 trials), 93% received fibrinolytic therapy. In the absence of aspirin, heparin therapy reduced mortality (11.4% vs. 14.9% in control group, RRR: $25 \pm 8\%$, 95% CI: 10% to 38%, $p = 0.002$), reduced stroke (1.1% vs. 2.1%, $p = 0.01$) and pulmonary embolism (2% vs. 3.9%, $p < 0.001$). There was a significant increase in major bleeds (2.3% vs. 1.1%, $p = 0.01$). In the presence of aspirin, adding UFH reduced mortality (8.6% vs. 9.1% in the aspirin-alone group, $p = 0.03$), and reinfarction (3% vs. 3.3% for aspirin alone, $p = 0.04$), but there was a significant excess of major bleeds (1% vs. 0.7%, $p < 0.0001$).

LMWH. LMWH has been extensively evaluated in prospective randomized trials of STEMI patients including those who did not receive any reperfusion therapy. The TETAMI trial (19) evaluated 1,224 STEMI patients who were not eligible for reperfusion therapy. Enoxaparin subcutaneously twice daily for 2 to 8 days was compared with intravenous UFH, with and without the glycoprotein IIb/IIIa receptor antagonist tirofiban, in a 2×2 factorial design. There were no significant differences between the enoxaparin and UFH groups in the combined incidence of death, reinfarction, or recurrent angina at 30 days, or in safety. Additional therapy with tirofiban was not beneficial.

In a pre-specified subgroup analysis of the CREATE (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation) (48), the LMWH reviparin was assessed versus placebo in 3,325 of the 15,570 STEMI patients (21%) who did not receive any reperfusion therapy. Reviparin twice daily for 7 days reduced the composite of death, myocardial reinfarction, and stroke at 7 days versus placebo in these nonreperfused patients (OR: 0.79, 95% CI: 0.65 to 0.95).

The OASIS-6 randomized trial evaluated the impact of daily fondaparinux during hospital stay, compared with standard approaches to anticoagulant therapy in a broad range of patients with STEMI treated with primary PCI, thrombolysis, or no-reperfusion therapy (14). In the subgroup of patients not receiving reperfusion therapy, fondaparinux as compared with usual care (UFH infusion or placebo) significantly reduced the composite of death or myocardial reinfarction without increasing severe bleedings or strokes (49).

Compared with UFH, these trials suggest that, in STEMI patients who present late or are ineligible for reperfusion therapy, LMWHs given along with aspirin provide significant benefit, and their use in these patients is

supported by both current European and North American STEMI guidelines (3,4,50).

PARENTERAL DIRECT THROMBIN INHIBITORS. The HERO (Hirulog and Early Reperfusion or Occlusion)-2 study (51) evaluated the role of direct thrombin inhibition as an adjunctive therapy to thrombolytics in STEMI. Adjunctive bivalirudin did not reduce mortality compared with UFH (10.8% vs. 10.9%), but was associated with a lower rate of adjudicated myocardial reinfarction within 96 h (1.6% vs. 2.3%, $p = 0.005$). There are no data available on the role of direct thrombin inhibitors in STEMI with no-reperfusion therapy.

Antithrombotic therapy with oral anticoagulants. The effect of anticoagulation therapy with warfarin on mortality and reinfarction after MI was studied by the Norwegian WARIS (Warfarin-Aspirin Re-Infarction Study) (52) and WARIS 2 (53) trials, which enrolled survivors of acute MI (STEMI and NSTEMI). In the WARIS, the majority of patients did not receive any reperfusion therapy, and warfarin use was associated with a 24% RRR in mortality, 34% RRR in nonfatal recurrent MI, and 55% RRR in cerebrovascular accidents compared with placebo. The absolute risk of serious bleeding increased by 0.6% per year in the warfarin-treated patients. Of note, 90% of the patients randomly assigned to the warfarin arm received therapy beginning at least 2 weeks after the index event. In the WARIS 2 study, 46% of patients did not receive any reperfusion therapy, and warfarin in combination with aspirin or given alone, was superior to aspirin alone in reducing the incidence of composite events after MI. The total number of events were 24.5% in the aspirin-alone group, 19.4% in the warfarin-alone group, and 17.4% in the combined-therapy group (mean international normalized ratio >2.0). In the similarly designed ASPECT-II (Aspirin and Coumadin After Acute Coronary Syndromes) trial (54), the combination therapy with aspirin and warfarin (mean international normalized ratio 2.4) provided a 50% RRR in the combined end point of death, MI, or stroke compared with aspirin alone (RRR: 0.5, 95% CI: 0.27 to 0.92) up to 26 months after MI. As emerged from these trials, the combination of moderate intensity warfarin and a low dose of aspirin was the most effective therapy for the prevention of recurrent ischemic events after MI. The slightly higher rates of major and minor bleed in both warfarin groups, as well as the need for frequent international normalized ratio measurements and dose adjustments with this agent, have limited the use of oral anticoagulants post-MI in the U.S.

Nonantithrombotic therapies: work-reducing therapies and others.

BETA-BLOCKERS. There is substantial evidence for the benefits of early beta-blockade in patients with STEMI and no contraindications. Benefits have been demonstrated for patients with and without concomitant fibrinolytic therapy and both early and late after STEMI. In the ISIS-1 (First International Study of Infarct Survival) study (55), patients with an acute MI treated with intrave-

nous atenolol demonstrated a 14% RRR in 7-day mortality compared with controls, and reductions in the rates of reinfarction, arrhythmia, and cardiac arrest. Despite the evidence of benefit from beta-blockers, findings from various studies indicate their considerable underuse after MI, with only 20% to 50% of eligible patients receiving them (56).

INHIBITION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM.

A number of large, randomized clinical trials have assessed the role of ACEI early in the course of acute MI. All trials in which ACEI were administered orally demonstrated a benefit in mortality. The ISIS-4 (Fourth International Study of Infarct Survival) trial (57) studied the effects of mononitrates, captopril, and intravenous magnesium on mortality and morbidity in patients with suspected acute MI. Patients were randomly allocated to receive mononitrate or placebo, captopril or placebo, or intravenous magnesium versus no treatment. Of the 58,050 patients, 92% had confirmed MI and the median time to treatment was 8 h, 79% had STEMI, 70% received thrombolytic therapy (predominantly streptokinase), and 94% received antiplatelet agents. The ISIS-4 study provided evidence that ACEIs reduce short-term and 1-year mortality in MI patients. In the GISSI-3 trial (58), >19,000 patients with either ST-segment elevation or depression were randomly assigned to lisinopril or to open control: 71% of the patients received fibrinolytic treatment, 84% received aspirin, and only 3% received other antiplatelet agents. There was a significant reduction in 6-week mortality in patients receiving lisinopril (OR: 0.88, 95% CI: 0.79 to 0.99). The SMILE (Survival of Myocardial Infarction Long-term Evaluation) study (59) involved 1,556 patients randomly assigned within 24 h to receive either placebo or zofenopril. The patient population was restricted to those with anterior MI who had not received fibrinolytic therapy. The early use of an ACEI in this trial conferred a trend of reduction in mortality in the first 6 weeks (RRR: 25%, $p = 0.19$). These data support the role of ACEI with or without reperfusion therapy in STEMI.

NITRATES. Clinical trials such as ISIS-4 (57) and GISSI-3 (58) have suggested only a modest benefit of nitrates when used acutely in STEMI. Nitrates are useful only for the treatment of recurrent angina, and should not be used if the subsequent hypotension limits the administration of beta-blockers or ACEI, which have more powerful benefits for STEMI patients.

STATINS. The early use of statins in ACS (STEMI and non-STEMI) reduces both short and long-term adverse outcomes such as subsequent cardiovascular mortality, MI, coronary revascularization, and stroke (3,4). Many ACS trials do not specifically report the use of statins, and the more recent statin trials were conducted in the setting of STEMI receiving reperfusion therapy.

Conclusions

Very few patients with STEMI present with true or relative contraindications for reperfusion therapy. If scientific evidence and clinical guidelines are applied diligently, the vast majority of STEMI patients should receive some form of reperfusion therapy. The ESTIM (Evaluation of Therapeutic Strategies for Myocardial Infarction) Midi-Pyrénées, a French multidisciplinary, prospective registry of patients with STEMI, demonstrated that it is possible to apply a revascularization strategy in as many as 89.4% of patients (60). Recently published data from a single French center with a systematic reperfusion policy showed that a reperfusion therapy can be implemented in as many as 96% of STEMI patients admitted within 6 h of symptoms, and this policy was associated with a significant decrease of in-hospital mortality (61).

For the treatment of late-presenting patients with STEMI (beyond the first 12 h after onset of symptoms), clinical evaluation and risk stratification represent the crucial elements guiding the choice of therapeutic intervention. In the presence of hemodynamic or electrical instability, and/or if the patient continues to experience symptoms, a reperfusion-based strategy using primary PCI is recommended and endorsed by the current guidelines (3–5). Among clinically stable, late-presenting patients, myocardial viability assessment and functional testing can identify yet another subgroup that may benefit from late mechanical reperfusion.

Pharmacological nonlytic therapy of patients with STEMI is clearly defined by the current practice guidelines, regardless of the reperfusion strategy or the absence of it. As in patients who receive reperfusion therapy, the nonreperused patients derive the most benefit from an appropriate antithrombotic regimen. Early initiation of dual-antiplatelet therapy with aspirin and a thienopyridine drastically reduces mortality and subsequent cardiovascular events in this population. Available data suggest that for patients who do not receive any form of reperfusion, anticoagulation therapy with LMWH provides a clear additional mortality benefit versus placebo. Fondaparinux as compared with usual care (UFH or placebo) significantly reduces the composite of death or myocardial reinfarction without increasing severe bleeding or number of strokes. Post-discharge chronic anticoagulation therapy post-STEMI is currently re-emerging, and with the advent of novel, safer oral anticoagulant agents (direct thrombin inhibitors or selective direct factor Xa inhibitors) (62,63), new clinical studies may demonstrate additional reductions in long-term cardiovascular events. Among work-reducing therapies, renin-angiotensin-aldosterone system modulation with ACEIs reduces early and late mortality in STEMI patients even in the absence of a reperfusion strategy. Chronic ubiquitous statin use after ACS provides a significant additional reduction in subsequent cardiovascular events.

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Key Words: coronary artery disease ■ antithrombotic therapy ■ STEMI.